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13. ABSTRACT *(Maximum 200 words)*

The rat pineal is a component of the circadian clock. Exogenous melatonin entrains the rat clock and does *not* require the presence of the pineal gland. The pineal gland is important for circadian rhythmicity. Pinealectomy exacerbates the disruptive effects of LL on rhythmicity. This may be due to a role of the pineal gland and melatonin in clock light sensitivity, since pinealectomized rats' periods decelerate more rapidly in increasing light than do those of sham-operated rats. It may also be due to a role in coupling circadian components since multiple outputs of the clock are disrupted by pinealectomy equivalently. The rat circadian clock regulates a plethora of peripheral processes by modulation of sympathetic tone. This regulation is responsible for the circadian rhythm in heart rate. The avian visual system contains high affinity melatonin receptors. These receptors are responsible for a circadian modulation of metabolic and electrical activity in visual structures. Melatonin receptors are regulated by the circadian clock. Receptor binding is rhythmic, high during the day and low during the night, does *not* depend on the pineal gland or melatonin but is abolished by lesions of the suprachiasmatic nucleus. Finally, we have cloned two melatonin receptors from chick brain.

14. SUBJECT TERMS

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Re: Final Technical Report - Grant 90-NL-0244

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YOU SHOULD RECEIVE 4 PAGE(S), INCLUDING THIS COVER SHEET. IF YOU DO NOT RECEIVE ALL THE PAGES, PLEASE CALL 409-862-4594.

The following is the Final Technical Report for Grant 90-NL-0244 for your reference. If you have any questions, please call 409-862-4594.

AFOSR-90-0244

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TEXAS A&M UNIVERSITY
Department of Biology

Dr. Genevieve Haddad
Program Manager
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Department of the Air Force
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July 12, 1995

Dear Dr. Haddad, GEN

I am writing the final report on Air Force Grant 90-NL-0244. This grant has been renewed under a new number, and therefore the original grant is being terminated.

I am very happy to say that we have been very productive with the funds your office has provided. In all we have published or are publishing 18 full-length papers listed below:

1) **Cassone, V.M.** (1991) Melatonin and SCN function. In: Suprachiasmatic Nucleus: The Mind's Clock. DC Klein, RY Moore, SM Reppert (eds) Oxford University Press, NY, pp. 309-323.

2) **Cassone, V.M.**, D.S. Brooks, (1991) The sites of melatonin action in the house sparrow brain. J. Exp. Zool. 260: 302-309

3) **Cassone, V.M.** (1992) The pineal gland influences rat circadian activity rhythms in constant light J. Biol. Rhythms 7: 27-40

4) Brooks, D.S., **V.M. Cassone** (1992) Daily and circadian regulation of 2[^{125}I]iodomelatonin binding in the chick brain. Endocrinology 131: 1297-1304

5) **Cassone, V.M.**, D.S. Brooks, D.B. Hodges, T.A. Kelm, J. Lu, W.S. Warren (1992) Integration of circadian and visual function in mammals and birds: brain imaging and the role of melatonin in biological clock regulation. In: Advances in Metabolic Mapping Techniques for Brain Imaging of Behavioral and Learning Functions. F. Gonzalez-Lima, T. Finkenstaedt and H. Scheich (eds) Kluwer Academic Publishers, Dordrecht/Boston/London, pp. 299-318.

6) **Cassone, V.M.**, W.S. Warren, D.S. Brooks and J. Lu (1993) Melatonin, the pineal gland and circadian rhythms. J. Biol. Rhythms 8, Suppl.: S73-S81

7) Warren, W.S., D.B. Hodges, **V.M. Cassone** (1993) Pinealectomized rats entrain and phase-shift to melatonin injection in a dose-dependent manner. J. Biol. Rhythms 8: 233-245

8) Lu, J. and **V.M. Cassone** (1993) Pineal regulation of circadian

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rhythms of 2-deoxy[^{14}C]glucose uptake and 2[^{125}I]iodomelatonin binding in the visual system of the house sparrow, Passer domesticus. J. Comp. Physiol. A 173: 765-774

9) Lu, J., and **V.M. Cassone** (1993) Daily melatonin administration synchronizes circadian patterns of brain metabolism and behavior in pinealectomized house sparrows, Passer domesticus. J. Comp. Physiol. A 173: 775-782

10) Warren, W.S., T.H. Champney and **V.M. Cassone** (1994) The suprachiasmatic nucleus controls circadian rhythms of heart-rate via the sympathetic nervous system. Physiol. Behav. 55: 1091-1099

11) **Cassone, V.M.**, and J. Lu (1994) The pineal gland and avian circadian organization: the neuroendocrine loop. Adv. Pineal Res. 8: 31-40

12) Warren, W.S., and **V.M. Cassone** (1995) The pineal gland, photoreception and coupling of behavioral, metabolic and cardiovascular circadian outputs. J. Biol. Rhythms 10: 64-79

13) **V.M. Cassone**, D.S. Brooks, and T.A. Kelm (1995) Comparative distribution of 2[^{125}I]iodomelatonin binding in the avian brain: outgroup analysis with turtles. Brain Behav. Evol. 45: 241-256

14) Lu, J., M.J. Zoran and **V.M. Cassone** (1995) Daily and circadian variation in the chick electroretinogram: Effects of melatonin. J. Comp. Physiol. 176:

15) Brooks, D.S. and **V.M. Cassone** (in press) The distribution of 2-[^{125}I]iodomelatonin binding during the development of the chick visual system Dev. Brain Res.

16) Reppert, S.M., D.R. Weaver, **V.M. Cassone**, C. Godson, A Roca and L.F. Kolakowski Jr. (in press) Melatonin receptors are for the birds: Molecular analysis of two receptor subtypes differentially expressed in chick brain. Neuron

17) Lu, J., H. Wu, and **V.M. Cassone** (in preparation) A mathematical model of the biological clock of birds J. Biol. Rhythms

18) Brooks, D.S., and **V.M. Cassone** (in preparation) Role of the pineal gland and visual suprachiasmatic nucleus in the circadian regulation of 2-[^{125}I]iodomelatonin binding in the chick brain.

In addition, with Air Force funding, we have directly funded three graduate students through their Ph. D. degrees. These students are listed below:

1) Dr. David S. Brooks is an Assistant Professor of Biology at LeTourneau University in Longview, TX.

2) Dr. Jun Lu is a post-doctoral fellow with Dr. Michael Menaker at the NSF Center for Biological Timing at the University of Virginia.

3) Dr. Wade S. Warren is just starting a post-doctoral fellowship with Dr. Timothy Bartness at Georgia State University.

We have also supervised 6 Master's level graduate students who have gone on to do great things:

1) Mrs. Alaana Tynes is an instructor of human physiology at Blinn Junior College.

2) Mrs. Teresa Kelm is a high school teacher at Waco High School.

3) Miss Dawn Parker is studying for a Ph.D. degree in Scientific Education at Texas A&M University.

4) Mr. Donald B. Hodges is a research assistant with Pfizer Pharmaceuticals.

5) Ms. Haydee Vercesi is a research assistant at SUNY at Stony Brook.

6) Mrs. Melissa G. Rucker is a research assistant in my laboratory here at Texas A&M.

Finally, we are currently supervising 2 Ph.D. level graduate students, who are doing great things.

1) Mr. Arjun Natesan is in his second year.

2) Mr. Hong Tao Min is in his first year.

Research on the original proposal continues. We are still working on the in vivo microdialysis research and should have a manuscript ready by the end of the year. We are also making great strides on the molecular biology of the melatonin receptor. As you can see from the list of publications, we have, in collaboration with Steve Reppert and others, cloned two melatonin receptors in chicks. One of the receptors is specific for glia and is expressed rhythmically in the pineal gland (but is not translated there!!). In addition, in collaboration with Dave Klein, we are working on the chick NAT molecule.

We have not forsaken the systems level physiology research you and I love so well. We are still working on the in vivo microdialysis, and Wade Warren has just finished a study of norepinephrine turnover in peripheral tissues of the rat. Rhythms of turnover are pervasive in the body, but have different phases. SCN lesion abolishes them!

Anyway, thank you for your continuing support. I hope and trust we can continue our productive relationship.

Sincerely Yours,

Vincent M. Cassone, PhD